#8
6/22/00
C. Styles

Patent
Attorney's Docket No. 017753-113

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
)
Jean-Pierre ROBIN et al.) Group Art Unit: 1611
)
Application No.: 09/270,006) Examiner: V. Balasubramanian
)
Filed: March 16, 1999)
)
For: NOVEL CEPHALOTAXANE)
DERIVATIVES AND PROCESS)
FOR THEIR PREPARATION)

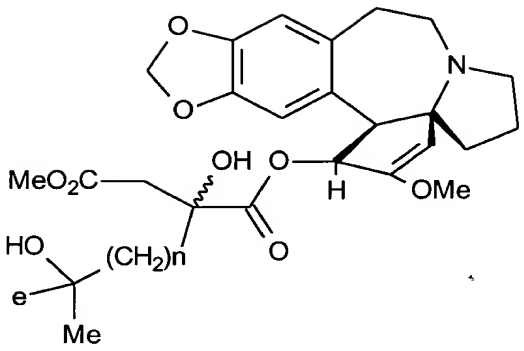
RESPONSE TO RESTRICTION REQUIREMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

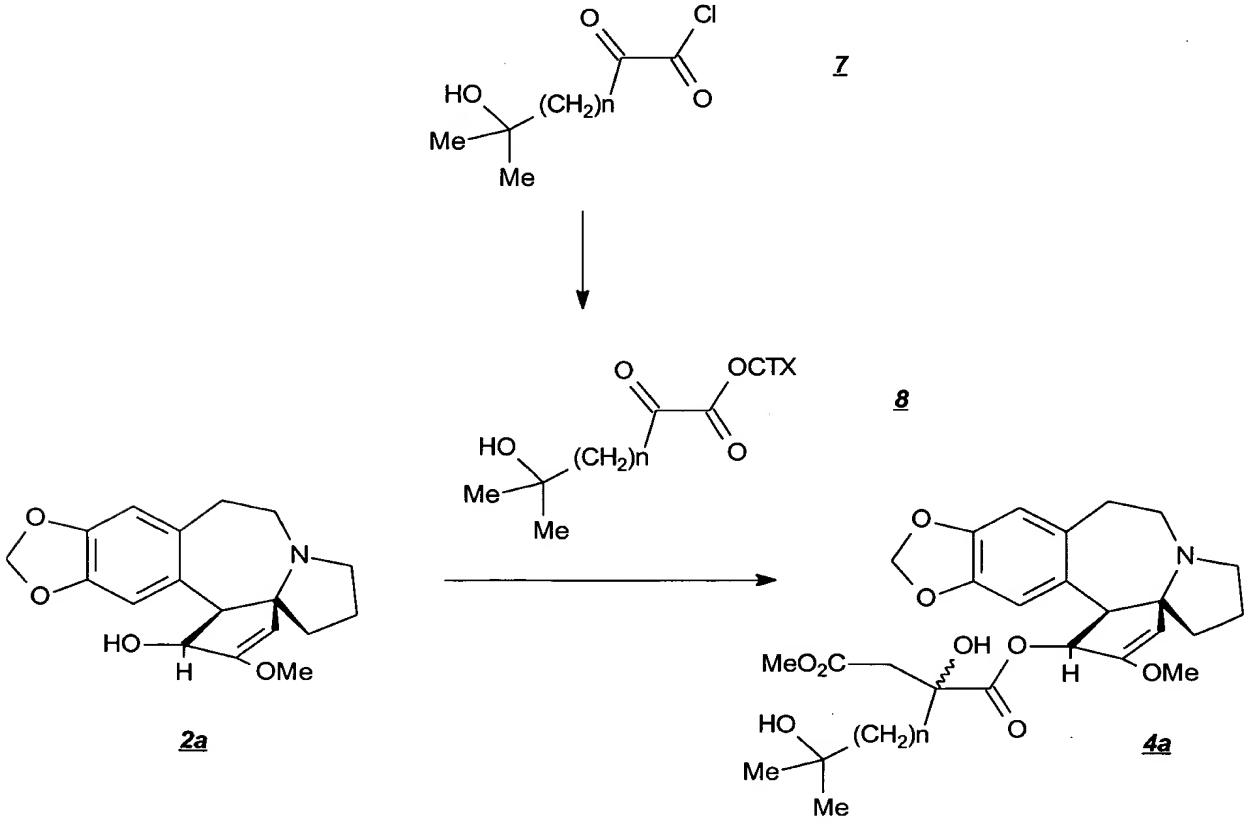
In complete response to the Official Action mailed on February 23, 2000, requiring restriction under 35 USC applicants hereby elect, albeit with traverse, the claims of group VI, claims 59-71, drawn to tertiary cycloalkane carboxylic acid compounds. The Restriction Requirement is traversed on the basis that the compounds claimed in groups IV, V, VI, and VIII, and in particular groups V, VI, and VIII, are related both structurally and functionally, as described below.

The presently claimed invention concerns a process for preparing cephalotaxane derivatives bearing a side chain. One of the most typical cephalotaxane derivatives is harringtonine ***4b*** .

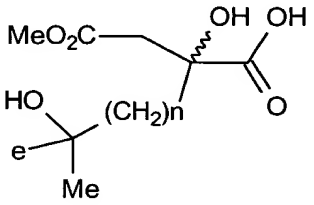


(structures of this and other compounds discussed below may be found at pages 8 *et seq.* of the present specification).

All methods for producing such compounds known in the prior art involved esterifying a cephalotaxine 2a with a keto-alkanoyl chloride (7 esterified to 8) which results in compound 4a.

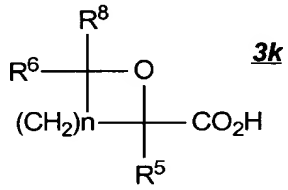


Compound 7 lacks the end hydroxyl because it has always been considered impossible to esterify a highly sterically hindered secondary hydroxyl of cephalotaxine 2a with the tertiary carboxyl of the alkanoyl chain of a harringtonic acid 3e totally preformed.



3e

The present inventors have suprisingly discovered that, in contrast to the teachings of the prior art, it is possible to esterify the 13-hydroxyl of cephalotaxines with an acid such as a 2-carboxyl-2-alkyl-1-oxacycloalkone derivative 3k



3k

(This and related compounds may be found at pages 12 *et seq.* of the present specification).

Therefore, the present invention relies on the discovery that it is possible to esterify the 13-hydroxyl of cephalotaxine with an acid, *e.g.*, of formula 3k. The present claims are all directed to variations of this basic theme.

It is well known in the art that, when performing an esterification reaction between an alcohol (R-OH) and an acid (R-COOH), that the esterification can be equally performed with (a) alcohols or alcoholates (R-OM, with M being a metal); or (b) acids or acid derivatives (commonly referred to as activated acid derivatives: R-COO A, A being a leaving group (acid halide, anhydride hemi-ester, etc.)).

In the case where the alcohol, and/or the acid have an asymmetric carbon, those skilled in the art studying an esterification reaction would also contemplate the

possibility of reacting specific pure enantiomers, diastereoisomers, and/or racemic mixtures.

The present inventors specifically investigated the use of chiral activated acid derivatives, i.e. chiral hemi-esters, and arrived at the esterification process of the present invention. The present claims thus covering the following equivalent embodiments:

$$\begin{bmatrix} \Omega\text{-COOH} \\ \Omega\text{-COA} \\ \Omega^*\text{-COOH} \end{bmatrix} + \begin{bmatrix} \text{CTX-OH} \\ \text{CTX-OM} \end{bmatrix} \rightarrow \Omega\text{-COO-CTX}$$

as well as the needed intermediates especially designed to perform such esterifications.

Put in these terms, the Restriction Requirement divided the present claims into the following groups:

Group I claims: process and product obtained Ω-COO-CTX

Group IV claims: intermediate CTX-OM

Group V claims: intermediate Ω*-COOH

Group VI claims: intermediate Ω-COOH

Group VIII claims: intermediate Ω*-COO-A

Intermediates of groups IV, V, Vi and VIII are new and specific to the preparation of new cephalotaxines derivatives. The esterification process of the present invention can only be conducted with the specific intermediates which are claimed. No other compound could react with the highly sterically hindered hydroxyl of cephalotaxane. Moreover, the claimed intermediates provide the essential structural elements present in the end-products.

In view of these facts withdrawal of the Restriction Requirement, and rejoinder of the claims of Groups I, IV-VI, and VIII, is respectfully requested. Alternatively, rejoinder of the claims of Groups IV-VI, and VIII, all of which are directed to intermediates useful in the production of the compounds of the claims of Group I, is believed to be appropriate. At the very least, Applicants respectfully

request that the claims of Groups V, VI, and VIII be rejoined, as the intermediate compounds claimed in these groups are all closely structurally related, as well as all being useful as intermediates in the production of the compounds of the claims of Group I.

In the event that there are any questions relating to this application, the Examiner is invited to telephone the undersigned so that prosecution of the subject application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Malcolm K. McGowan

Malcolm K. McGowan, Ph.D.
Registration No. 39,300

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620
Date: June 13, 2000